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311 St. Dunstan's Road
Baltimore, Maryland 21212
June 14, 1999

Dr. Jane Henney, Commissioner
U.S. Food and Drug Administration
5600 Fisher's Lane, Room 1471
Rockville, Maryland 20857

Dear Dr. Henney:

For some years an appreciable number of physicians have been concerned about the adverse effects of administration of antibiotics to animals intended for food consumption.

Recently there have been an increasing number of bacteria which seem to be relatively immune to the antibiotics usually administered to humans for treatment. We, as physicians, are partly responsible by overuse of antibiotics for unnecessary purposes. However, the use of antibiotics in animals, solely for the purpose of improving the yield, has also been indicted in causing the development of antibiotic-resistant strains of bacteria. Enclosed is a recent editorial from the New England Journal of Medicine expressing concern about the use of quinolones in food animals.

Their use in agribusiness is primarily one of pecuniary advantage. The use in humans is a live-saving one in many instances. The use in the former should be banned to save human lives.

Sincerely yours,

James E. Smith II, M.D.

JES:RH
CC: President William Clinton
Senator Paul Sarbanes
Senator Barbara Mikulski

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Editorials

The Consequences for Food Safety of the Use of Fluoroquinolones in Food Animals

In June 1998, the World Health Organization convened a meeting to discuss the use of quinolones in animals used for food and its potential effect on human health. Participants included experts from a wide range of disciplines.[1] They concluded that major gaps in the data need to be filled in order for them to assess the public health implications of the use of quinolones in animals used for food.

The report by Smith et al. in this issue of the *Journal*[2] adds new and valuable information that fills some of those gaps. The report links an increase in domestically acquired quinolone-resistant *Campylobacter jejuni* infections (i.e., those acquired in the United States) in Minnesota from 1992 through 1998 to the licensing of fluoroquinolones for use in poultry production in the United States in 1995. The investigators detected a high prevalence of quinolone-resistant campylobacter in retail chicken products produced domestically. They documented DNA fingerprints in quinolone-resistant *C. jejuni* from domestically produced poultry that were identical to those in the resistant *C. jejuni* from domestically acquired infections in humans. Previous studies in Europe have shown similar trends in the incidence of quinolone-resistant human infections after quinolones were licensed for use in food animals.[3,4] The report by Smith et al. adds to the growing scientific evidence that the use of quinolones in food animals leads to the development of resistant pathogenic bacteria that can reach humans through the food chain.

In the Minnesota study, patients infected with resistant *C. jejuni* who were treated with fluoroquinolones were found to have a longer duration of diarrhea than were patients with fluoroquinolone-sensitive isolates (an average of 10 days vs. 7 days). Thus, a public health effect of the use of quinolones in animals was identified. Three extra days of diarrhea in otherwise healthy patients may be regarded as a mild complication of a treatment failure, but campylobacter infection is among the most common causes of bacterial gastroenteritis in developed countries; the economic consequences in terms of loss of productivity at work are therefore substantial. More important, campylobacter infections can be serious in vulnerable patients with underlying health problems. For immunocompromised patients who have invasive campylobacter infections, treatment failure can be fatal.

Increasing foreign travel and the internationalization of the food trade make the use of antibiotics in food production a public health issue of global dimensions. Campylobacter is one of the most common causes of traveler's diarrhea in developed countries, and infections with quinolone-resistant strains are being found with increasing frequency in this clinical setting.[5] That foreign travel is an important risk factor for acquiring a quinolone-resistant *C. jejuni* infection in the United States is therefore not surprising. In the Minnesota study, the majority of travel-related cases of resistant infections were associated with travel to Mexico. Smith et al. present data on quinolones in animals used for food in Mexico. The sale of quinolones for use in poultry amounted to 326 million medicated liters in 1997 (which I assume means medicated water). Mexico produced 1.5 billion kg (3.2 billion lb) of chicken meat in 1997, which must be about 500 million to 1 billion slaughtered chickens. Consequently, a chicken in Mexico consumes on average approximately half a liter of quinolone-medicated water. The exposure probably produces a high pressure for the selection of quinolone-resistant *C. jejuni* in Mexican poultry production.

The report by Smith et al. has a message for both veterinarians and physicians. The treatment of human campylobacter infection with quinolones was found to be a risk factor for resistant infections. This finding is in agreement with results from other countries showing that *C. jejuni* is prone to develop resistance during treatment.[6] We generally accept the development of resistance as a side effect of the necessary antibiotics. But how often is treatment necessary? Smith et al. report that 83 percent of all patients with campylobacter infection were treated with an antibiotic. This represents a very high proportion of patients. In a case–control investigation recently conducted by the Danish Zoonosis Center and State Serum Institute, it was found that less than 10 percent of 459 Danish patients with campylobacter infection had been treated with antibiotics (Neimann J: personal communication). Physicians' prescribing practices for the same conditions differ a great deal among countries. The situation described in Minnesota represents massive overprescribing. Treatment should be restricted to early empirical treatment of severely ill and vulnerable patients who have underlying health problems. Physicians and veterinarians have a shared responsibility to help prevent the development of resistance in foodborne pathogens.

In recent years, concern about the public health consequences of the use of antibiotics in food animals has grown.[7,8] Foodborne bacterial pathogens have become increasingly resistant to antibiotics, resulting in increased human morbidity and mortality. Such an increase has been documented for salmonella, with *S. typhimurium* definitive type 104 as a recent example,[9,10] and now also for *C. jejuni*. Fur-

thermore, the emergence and spread of the virtually untreatable vancomycin-resistant *Enterococcus faecium* infections in hospitals have been linked to the use of glycopeptides in food animals.[11]

Nearly all the antibiotics available for human therapy, and several classes likely to be made available for humans in the future, are being used in food animals. The development of new antibiotics for human use has slowed, and the drugs most recently licensed for use in food animals belong to the same classes as those still considered the most potent antibiotics for humans, including fluoroquinolones and third-generation cephalosporins. Furthermore, pharmaceutical companies often rediscover old drugs in their quest for new drugs. Some of the antibiotics that in earlier days had little potential for human use were used as growth promoters in animals instead — streptogramins and everninomicins, for example. Pharmaceutical companies are now developing these same compounds for human use, but decades of use in animals have created a huge reservoir of resistant bacteria and resistance genes in animals used for food, with a potential to spread to humans.

In modern production of food animals large amounts of antibiotics are used for therapy, prophylaxis, and growth promotion. Much of this use can be reduced by the development of better feeding practices and production systems that promote animal health and welfare. In Denmark, the total amount of antibiotics used in food animals in 1994 was 205 tons: 90 tons for therapy and prophylaxis and 115 tons for growth promotion. By the year 2000, this use will have been reduced to approximately 50 tons by the combined effects of legislation, voluntary discontinuation of the use of antimicrobial growth promoters, and new antimicrobial-prescribing guidelines for practicing veterinarians. This reduction is taking place with no apparent adverse effects on animal health and welfare or on the income of the producers.

If we do not want to lose the effect of quinolones for empirical treatment of gastrointestinal infections in humans, the use of quinolones in animals must be limited as much as possible. Quinolones should be used for the treatment of animals only when all other therapies have failed. Furthermore, quinolones should not be licensed for use in animals for indications for which therapeutic alternatives are available, at least until alternatives to the quinolones have been developed for the empirical treatment of gastrointestinal infections in humans. The agricultural industry should be aware that in the future, foodstuffs containing quinolone-resistant bacterial pathogens may be considered unfit for human consumption.

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CALCIFIC TENDINITIS OF THE SHOULDER

CALCIFIC tendinitis of the shoulder is a self-limiting calcification of the rotator cuff (Fig. 1). Radiologically evident calcification has been reported in 7.5 to 20 percent of adults with no symptoms[1,2] and in 6.8 percent of those with shoulder pain.[2] The disorder is most common among people between 30 and 60 years of age. Women are slightly more likely to be affected than men, and workers in sedentary jobs appear to be at higher risk than those in manual work. Bilateral involvement is not uncommon.

The reason for the deposition of calcium hydroxyapatite crystals in the tendon is unclear. The condition may be related to fibrosis and necrosis of the tendon, with subsequent degeneration.[3] Others have proposed that the disorder is nondegenerative.[4] The disorder has four stages. The first (the precalcific phase) involves asymptomatic fibrocartilaginous transformation within the tendon. In the second stage (the formative phase), calcification develops within the cuff. This process may produce no symptoms or may be associated with variable degrees of pain at

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